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| EXAMINER |
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HOLLERAN, ANNE L

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| ART UNIT | PAPER NUMBER |
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1643

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|----------------------------------------|------------|---------------|
| 3 MONTHS | 03/14/2007 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/648,816

Applicant(s)

VAN BRUGGEN ET AL.

Examiner

Anne L. Holleran

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 December 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-21 and 30-44 is/are pending in the application.
- 4a) Of the above claim(s) 7-10 and 15-18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-6,11-14,19-21 and 30-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. The amendment filed 12/21/2006 is acknowledged. Claim 2, and 22-29 were canceled. Claims 39-44 were added.

2. Claims 1, 3-21 and 30-44 are pending. Claims 7-10, and 15-18, drawn to non-elected inventions, are withdrawn from consideration.

Claims 1, 3-6, 11-14, 19-21, and 30-44 are examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections/Rejections Withdrawn:

Claim Objections

4. The objections to claims 32-34 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of the amendment to the claims.

5. The rejection of claim 1 under 35 U.S.C. 102(e) as being anticipated by either Jirousek (U.S. 6,093,740; issued July 25, 2000; effective filing date Apr. 30, 1997) or Aiello (U.S.

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6,114,320; issued Sep. 5, 2000; effective filing May 1, 1996) is withdrawn in view of the amendment.

6. The rejection of claims 1 and 11-13 under 35 U.S.C. 102(b) as being anticipated by Aiello-II (Aiello, L.P., et al, Proceedings of the National Academy of Sciences. USA, 92: 10457-10461, 1995) as evidenced by Aiello (supra) as evidenced by Aiello (supra) is withdrawn in view of the amendment to the claims.

Claims Rejections Maintained and New Grounds of Rejection:

Claim Rejections - 35 USC § 112

7. Claim 31 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record.

Applicants' arguments have been considered, but fail to persuade. Additionally, the passage pointed to by applicants of page 24, lines 11-17 does not appear to refer to edema due to conditions that can involve the central nervous system, but instead appears to be a discussion of different formulations for hVEGF antagonists. Also, applicants argue that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. However, claim 31 was introduced in a preliminary amendment filed (12/08/2003) after the filing date of the instant application (8/26/2003). The amendment to claim 31 fails to obviate the rejection. The basis of the rejection is not that the specification fails to

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teach the conditions listed in claim 31, but that the specification does not teach these conditions as associated with central nervous system edema, only with edema in general. Because claim 31 is dependent from claim 30, which is limited to treatment of edema that is central nervous system edema, claim 31 now encompasses treating central nervous system edema associated with the conditions listed in claim 31, and support for this concept is not found in the specification as originally filed.

8. Claims 41 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the amendment, filed 12/21/2006, which introduces claims 41 and 44, introduces new matter into the specification as originally filed.

As a preliminary matter it is noted that applicants point to pages 23-25 and Example 7 as support for the amendments to the claims. These passages were reviewed, and support for the concept of administering an hVEGF antagonist within about four days of identification of the presence of cerebral edema was not found. Example 7 provides the only teachings of timing of administration of an hVEGF antagonist. In example 7, the antagonist that is administered is an hVEGF receptor fusion protein (flt-IgG). The antagonist is administered 12 hours before a surgery that produced focal cortical ischemia by occlusion of the middle cerebral artery, and at the time of reperfusion and again at 1 and 2 days following surgery. While this may be one example of administration that occurs within 4 days of identification of cerebral edema, where

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the example is very specific in timing, and nature of insult (middle cerebral artery occlusion for 45 minutes), there is no contemplation in the specification for the broad time period of within 4 days of identification of cerebral edema due to any type of non-neoplastic condition (which may includes head injury, spinal cord injury, acute hypertension, meningitis, encephalitis, abscess, hemorrhage, viral infection, cerebral malaria, radiation, multiple sclerosis, cardiac arrest, birth asphyxia, glutamate toxicity, encephalopathy, hypoxia, ischemia or renal dialysis). Additionally, the range of “within 4 days” of identification of cerebral edema encompasses a broad range of possible administration times and patterns that are not similar or envisioned from the one very specific example provided by experimental protocol of Example 7. Contemplation of time periods for administration was also found at page 28, lines 11-14. These teachings were specific for cerebral edema or stroke, and the contemplation was that the hVEGF antagonist would be administered immediately upon detection or diagnosis in the patient, within several hours of injury or onset of stroke or within 1 to 4 days thereafter. These teachings are also not commensurate in scope with the phrase “within four days of identification of cerebral edema”, because this phrase may include four days before cerebral edema, whereas the specification contains the teaching of within 1 to 4 days after the injury or onset of stroke. Therefore, the introduction of the concept of administration of an hVEGF antagonist “within four days of identification of cerebral edema” broadens the scope of the disclosure of timing for antagonist-administration from what was originally contemplated. Therefore, claim 42 introduces new matter into the specification as originally filed.

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9. Claims 1, 6, 30, 31, 36-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of cerebral edema that is associated with brain tumor, stroke or head injury, does not reasonably provide enablement for CNS edema associated with any condition, any non-neoplastic condition, or for cerebral edema associated with any non-neoplastic condition, or for the prevention of cerebral edema during a stroke (claims 6 and 14, "having a stroke"). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is that the specification fails to provide adequate guidance for the use of hVEGF antagonists that inhibit the interaction of an hVEGF with an hVEGF receptor for the treatment of patients that have edema and also non-neoplastic conditions such as spinal cord injury, acute hypertension, meningitis, encephalitis, abscess, hemorrhage, viral infection, cerebral malaria, radiation, multiple sclerosis, cardiac arrest, birth asphyxia, glutamate toxicity, encephalopathy, hypoxia, ischemia or renal dialysis.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The claimed methods are broadly drawn to treatment of mammals having edema due to any non-neoplastic condition comprising administering to the mammal an effective amount of an

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hVEGF antagonist that inhibits interaction of an hVEGF with an hVEGF receptor. The claimed methods appear to encompass methods of prevention of edema because claims 6 and 14 recite that mammal is “having” a stroke, which is differentiated from “having undergone a stroke”. Furthermore, the specification contemplates administration of an hVEGF antagonist within several hours of injury or stroke (see page 28, lines 11-12), which would include a time period before the injury or stroke. The non-neoplastic conditions that may produce the edema may be head injury, spinal cord injury, acute hypertension, meningitis, encephalitis, abscess, hemorrhage, viral infection, cerebral malaria, radiation, multiple sclerosis, cardiac arrest, birth asphyxia, glutamate toxicity, encephalopathy, hypoxia, ischemia or renal dialysis. Therefore, in addition to treating a patient having undergone a stroke or having a head injury, the claimed methods may be used for preventing a stroke or for the treatment of patients with spinal cord injury, acute hypertension, meningitis, encephalitis, abscess, hemorrhage, viral infection, cerebral malaria, radiation, multiple sclerosis, cardiac arrest, birth asphyxia, glutamate toxicity, encephalopathy, hypoxia, ischemia or renal dialysis. Thus, the population of patients to be treated is a population of patients having a diversity of conditions, whereas the population of mammals that are exemplified for the treatment of edema is that of a mouse having the middle cerebral artery occluded for 45 minutes.

Other than to list the multiple examples of non-neoplastic conditions cited above, the specification provides no guidance for methods of treating populations of patients having these conditions other than to contemplate treating edema or central nervous system (CNS) edema that might be associated these conditions. There is no analysis for whether the treatment of the edema part of the condition would be contraindicated by any other symptoms that may arise

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from having any one of these conditions. Furthermore, the working example that is related to demonstrating the effects of a VEGF antagonist for the treatment of cerebral edema due to stroke is a very specific example of brain edema caused by a surgery that produces focal cortical ischemia by occlusion of the middle cerebral artery. This working example is not commensurate in scope with the scope of the injuries and conditions that are encompassed by injury, spinal cord injury, acute hypertension, meningitis, encephalitis, abscess, hemorrhage, viral infection, cerebral malaria, radiation, multiple sclerosis, cardiac arrest, birth asphyxia, glutamate toxicity, encephalopathy, hypoxia, ischemia or renal dialysis.

Because the claims are drawn to treating the mammal having edema due to any one of these conditions, the claims encompass treating mammals having such conditions, and these conditions may encompass symptoms other than edema, which may not be treatable by administration of VEGF antagonists and which for the administration of a VEGF antagonist may be contraindicated. Thus, for the treatment of conditions other than stroke or head injury, the specification lacks adequate guidance for use of VEGF antagonists in methods of treatment because the working example is narrowly concerned with a specific model of stroke that causes brain edema, whereas the claimed methods are broadly drawn to methods of treatment or prevention of a wide variety of conditions and diseases.

10. Claims 1, 3-5, 11-13, 39 and 40 remain rejected under 35 U.S.C. 102(b) as being anticipated by Ferrara (WO 94/10202; published 11 May 1994; cited in the IDS).

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The claimed method are drawn to methods of treating edema, or cerebral edema, or edema associated with neoplastic disease, such as a brain tumor, comprising the administration of hVEGF antagonists, where the hVEGF antagonists may be hVEGF receptor fusion proteins.

Ferrara teaches methods of treatment comprising administering hVEGF antagonists, where the hVEGF antagonist may be a flt-IgG fusion protein (see page 22, lines 10-33; claim 30; page 2, line 29-page 3, line 4). Ferrara also teaches combination therapy (see page 17, lines 15-28). Thus, Ferrara teaches methods that are the same as that claimed, because the active step of the claimed methods are the same as the active step of the methods taught by Ferrara. Furthermore, it appears that Ferrara appreciated that hVEGF antagonists would be useful in the treatment of diseases or disorder characterized by undesirable vascular permeability, such as edema associated with a brain tumor. Thus, Ferrara teaches methods that are the same as that claimed.

Applicants argue that the claimed methods are not anticipated by Ferrara because the patient population is different from the patient population of the claimed methods and because Ferrara teaches that the hVEGF antagonists may be used to treat angiogenesis and not edema.

This is not found persuasive because the patient population in both cases is a patient having a brain tumor and edema and because in both cases hVEGF antagonists are administered. Furthermore, Ferrara teaches that hVEGF antagonists would be useful in the treatment of diseases or disorder characterized by undesirable vascular permeability, such as edema associated with a brain tumor.

Claim Rejections - 35 USC § 103

11. Claims 1, 6, 14-21, 30-38, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara (supra) in view of Bates (Bates, D.O. et al. Am. J. Physiol. 271: H2520-H2528, 1996) and further in view of Aiello (U.S. 6,114,320; issued Sep. 5, 2000; effective filing May 1, 1996) or Ozaki (Ozaki, H. et al. Exp. Eye Res. 64: 505-517, 1997; cited in IDS).

The claimed inventions include within their scope methods of treating cerebral edema, or stroke, where the cerebral edema is due to a non-neoplastic condition such as stroke or head injury, which may be ischemic stroke.

Ferrara teaches methods of treatment comprising administering hVEGF antagonists, where the hVEGF antagonist may be an anti-hVEGF monoclonal antibody (see page 22, lines 10-33; claim 28; page 2, line 29-page 3, line 4). Ferrara also teaches combination therapy (see page 17, lines 15-28). Furthermore, it appears that Ferrara appreciated that hVEGF antagonists would be useful in the treatment of diseases or disorders characterized by undesirable vascular permeability, such as edema associated with a brain tumor. Ferrara teaches methods of treating diseases or disorders associated with edema, but fails to specifically identify disorders such as the non-neoplastic condition of ischemic stroke or head injury. However, Aiello teaches that ischemia plays a role in the development of vascular permeability because ischemia stimulates the synthesis and secretion of growth factors such as VEGF in retinal pericytes, endothelial cells, the retinal pigment epithelium, glial cells and possibly other cell types and subsequently leads to retinal neovascularization and increased capillary permeability. Additionally, Bates teaches that VEGF increases hydraulic conductivity of isolated perfused frog microvessels to act both acutely

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and chronically to increase microvascular permeability (see abstract). Furthermore, Ozaki teaches that VEGF has a direct effect on retinal blood vessels to increase vascular permeability to both fluid and serum proteins and that VEGF causes blood-retinal barrier breakdown (see page 515, 2nd column to page 516, bridging paragraph). Ozaki also suggests that VEGF antagonists may be useful for the treatment of macular edema that is caused by ischemic retinopathies (diabetic retinopathy, branch vein occlusion, central retinal vein occlusion). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Ferrara to treat cerebral edema due to non-neoplastic conditions such as ischemic stroke or head injury. One would have been motivated to have used Ferrara's method because Ferrara's method targets VEGF, which is taught by Aiello to be induced by conditions such as hypoxia and which is taught by Bates and also Ozaki to have a direct effect on microvascular permeability.

The previous rejection is withdrawn in view of the new rejection above, however applicants' arguments for withdrawal of the previous rejection of the claims under 35 U.S.C 103(a) are considered. Applicants' attention is also drawn to a teaching of the present specification (page 26, lines 22-29) in which edema is taught to be either vasogenic edema, associated with a disruption of the blood-brain barrier, or cytotoxic edema, which is associated with an intact blood brain barrier. Applicants assert that one of ordinary skill in the art would not have understood at the time the invention was made that Ferrara's hVEGF antagonists could be used in the treatment of edema due to non-neoplastic conditions or cerebral edema due to non-neoplastic conditions, because there was no evidence that VEGF was the direct cause of cerebral edema and further that there was contradictory evidence that VEGF was involved in cerebral

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edema. Applicants draw examiner's attention to a copy of a declaration filed in the parent of the present application, in which Dr. Van Bruggen presents arguments that the association between VEGF and edema was contradictory. This is not found persuasive because Bates teaches that VEGF has a direct effect on microvessels to increase vascular permeability. Furthermore, Ozaki teaches that VEGF has a direct effect on retinal blood vessels to increase vascular permeability to both fluid and serum proteins and that VEGF causes blood-retinal barrier breakdown (both indications of "vasogenic edema"). Ozaki also suggests that VEGF antagonists may be useful for the treatment of macular edema that is caused by ischemic retinopathies (diabetic retinopathy, branch vein occlusion, central retinal vein occlusion). Thus, these teachings together with the teaching by Aiello that various cell types (including glial cells), in response to hypoxia, produce factors such as VEGF that lead to increased vascular permeability would have directed one of ordinary skill in the art to use Ferrara's hVEGF antagonists to treat edema due to a non-neoplastic condition.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the

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status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
March 11, 2007



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SUPERVISORY PATENT EXAMINER